

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIMETHYLDITHIOCARBAMATE, SODIUM AND POTASSIUM SALTS

Chemical Codes # 001934 and 548, Tolerances 52063 and 152

Original date: January 16, 2002, revised June 14, 2002 and August 14, 2002

The sodium (CC 548) and the potassium (CC 1934) salts of dimethyldithiocarbamate are grouped by US EPA (See the "Rainbow Report" of 1998).

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted.
Subchronic oral, rat:	No data gap, no adverse effect (Na)
Subchronic dermal, rabbit:	No data gap, dermal effects (Na)
Subchronic dermal, rat:	No data gap, dermal effects (K)
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted.
Oncogenicity, mouse:	Data gap, no study submitted.
Reproduction, rat:	Data gap, no study submitted.
Teratology, rat:	No data gap (K and Na), no adverse effect (K and Na)
Teratology, rabbit:	No data gap (K and Na), possible adverse effect (K)
Gene mutation:	No data gap (K and Na), possible adverse effect (K and Na)
Chromosome effects:	No data gap, possible adverse effect (Na) <sup>1</sup>
DNA damage:	No data gap (K and Na), no adverse effect (K and Na)
Neurotoxicity:	Not required at this time

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File name: T020814 comb

<sup>1</sup> Although there is no single acceptable study for either the potassium or the sodium salt, there are several studies which when considered collectively, fulfill the data requirement. (Gee, 6/13/02)

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### CHRONIC TOXICITY, RAT

No study submitted.

Subchronic:

\*\* 152 - 031 130890 Siglin, J. C. "91-Day Dermal Toxicity Study in Rats with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.15, August 12, 1988.) Busan 85 [50% potassium dimethyldithiocarbamate formulation] was administered dermally at doses of 0 (water), 75, 350 or 750 mg/kg/day, 6 hours/day, five days/week for 13 weeks, to 10 Sprague-Dawley rats/sex/group. Body weight and food consumption were reduced significantly for high-dose males, but only slightly for high-dose females. Erythrocyte counts were decreased and correlated with the increased incidence of splenic hemosiderosis for the high-dose group. The skin at the site of application was irritated for mid and high-dose groups with increases in the incidences of erythema, desquamation, eschar and discoloration. Microscopic examination confirmed acanthosis, epidermal exudate and ulcers. Dermal NOEL = 75 mg/kg/day. Systemic NOEL = 350 mg/kg/day (body weight, hematology). Evaluated as unacceptable, possibly upgradeable with verification of the preparation of the dosing material and doses of the active ingredient used. (Kishiyama and Gee, 7/19/01). Record 186644 (see below) in 52063 - 006 upgrades the study to ACCEPTABLE status. No worksheet. (Gee, 8/14/02).

52063 - 001 Same study as above but missing pages 90 - 120.

52063 - 006 186644 Supplement to record 130890, 91-day rat dermal study. The record contains a letter from J. C. Siglin, Springborn Laboratories, dated April 9, 2002, confirming that the active ingredient was potassium dimethyldithiocarbamate. The letter further describes how the dosing material was prepared, using a test article of 50% active ingredient. The Busan 85 was diluted to give 300 mg/ml w/v, 30%, without adjusting for actual content of the potassium dimethyldithiocarbamate. Therefore, actual doses of the ai need to be adjusted for dose preparation when determining a NOEL/LOEL for the study. This explanation upgrades record 130890 to acceptable status. No worksheet. (Gee, 8/14/02).

### CHRONIC TOXICITY, DOG

No study submitted.

### ONCOGENICITY, RAT

No study submitted.

## ONCOGENICITY, MOUSE

No study submitted.

## REPRODUCTION, RAT

No study submitted.

## TERATOLOGY, RAT

**\*\* 52063 - 003 136925** Rodwell, D. E. "Teratology Study in Rats with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.17, August 31, 1988.) Busan 85 (lot 7-0726, 50% a.i., 50% water) was given at doses of Busan 85 of 0, 0, 25, 150 or 400 mg/kg/day via gavage during gestation days 6 through 15 to 28 mated female Sprague-Dawley rats/group. The dosing material was not corrected for chemical purity, therefore the doses of potassium dimethyldithiocarbamate presumably would be approximately 50% of the nominal doses. Clinical signs of treatment were mostly confined to the mid and high dose groups, with dark material around the nose and mouth, rough coat, salivation being increased, among others. Dose-related lower body weight and food consumption were seen in the mid and high dose groups, especially days 6 - 9. Maternal NOEL = 25 mg/kg/day (clinical observations including salivation and dark material around mouth at 150 mg/kg, lower body weight at 400 mg/kg). Fetal effect of reduced weight was noted for the high dose group, although not statistically significant (3.3 g versus 3.7 g). Developmental NOEL = 150 mg/kg/day. There was no treatment-related increase in malformations/variations. No adverse effect. ACCEPTABLE. (Kishiyama and Gee, 1/10/02).

50282 - 14 074568: Same study as 052063-002 136925.

## TERATOLOGY, RABBIT

**\*\* 52063 - 002 136924** Rodwell, D. E. "Teratology Study in Rabbits with Busan 85". (Springborn Life Sciences, Inc., SLS Study No. 3138.19, September 20, 1988.) Busan 85 (lot 7-0726, 50% a.i., 50% water) was given by gavage at doses of 0, 0, 25, 75 or 150 mg/kg/day during gestation days 6 through 18 to 20 artificially inseminated New Zealand White female rabbits/group. The dosing material was not adjusted for chemical purity, therefore, the actual doses of potassium dimethyldithiocarbamate were approximately 50% of the Busan 85 dose. One and two does died at 75 and 150 mg/kg/day, respectively; one and two does aborted at these same doses. These were considered to be related to treatment. Reduced bodyweight gain or weight loss were dose-related for mid and high dose groups. Live litter size was reduced for mid-dose (3.5) and the high dose (0.5\*\*) groups compared with the two control groups (4.9 and 4.6). This was related to the increase in post-implantation loss. Early resorptions were increased, the means being 2.0\*\* and 3.8\*\* at the mid and high doses versus 0.4 and 1.7 for the two control groups. Although mean fetal weight was lower at the mid (41.1 g) and high (37.9 g) doses compared with controls (46.5 g and 47.6 g), the values were not statistically significant. The historical control data indicated a mean fetal weight of 41.6 g. The litter incidence of several malformations, especially skeletal, increased at 75 mg/kg/day (4\* litters versus 0 and 3 in the control litters for *total* skeletal malformations). At the high dose, only 4 fetuses were evaluated and no meaningful data were collected. Skeletal variations were also increased in incidence in litters. These effects were seen in the presence of maternal toxicity (abortion, death, lower weight gain, post-

implantation loss) and may be related to the maternal effects. Maternal and Developmental NOEL = 25mg/kg/day. Possible adverse effects. (early resorptions, total litter loss, increase in skeletal malformations/variations at 75 mg/kg with no preponderance of any specific finding). ACCEPTABLE (Kishiyama and Gee, 1/11/02).

50282-14 074567. Same study as 052063-002 136924.

## GENE MUTATION

**\*\* 52063 - 004, 007 136926, 186858** Young, R. R. "Mutagenicity Test on Busan 85 Lot Number 7-2020 in the CHO/HGPRT Forward Mutation Assay". (Hazleton Laboratories America, HLA Study No.: 10281-0-435, September 16, 1988.) Busan 85 (lot 7-2020, purity not given) was tested at concentrations ranging from 0.1 to 30 µg/ml without metabolic activation and from 1 to 25 µg/ml with rat liver metabolic activation for induction of forward mutations at the HGPRT locus in Chinese hamster ovary cells. Data were reported from two trials with activation and three trials without activation. At each concentration, there were duplicate cultures for mutation induction and three cultures for cytotoxicity. Exposure was for 4 hours. After 7 days for expression, each culture was plated in dishes for mutation frequency, for a total of 12 dishes, with 6-thioguanine for selection and in three dishes for cloning efficiency. Mutant frequency was increased above the normal background level with Busan 85 only at toxic concentrations, both with and without metabolic activation. Evaluated as unacceptable, upgradeable with purity of the test article. (Kishiyama and Gee, 1/9/02). Purity of lot 7-2020 was 52.2%. Additional information upgraded the study to ACCEPTABLE status. No new worksheet. (Gee, 6/13/02)

**\*\* 52063-004, 007 136929, 186859** Jagannath, D. R. "Mutagenicity Test on Busan 85 in the Ames *Salmonella*/Microsome Reverse Mutation Assay". (Hazleton Laboratories America, Inc., Laboratory Project ID HLA Study No.: 9970-0-401, October 30, 1987.) Busan 85 (lot 7-0726, 50% a.i.) was evaluated for mutagenic activity at concentrations ranging from 0.01 to 5.0 µl/plate using *Salmonella typhimurium* strains TA 98, TA100, TA1535, TA1537 and TA1538. There were triplicate plates per concentration with and without rat liver activation. The assay was repeated with strains TA100 and TA1535. The author states that there were an increased number of revertants with *Salmonella* strains TA 100 and TA1535 with and without S9 Mix. The repeat trial confirmed results of the initial trial. An independent evaluation could not be conducted because all the pages containing data were not included (pages 21 onward). Evaluated as unacceptable. Upgradeable with submission of missing pages. (Kishiyama and Gee, 1/9/02) Record number 186859 contains pages 21 through 34. Review of the data confirm the increase in revertants in strains TA1535 and TA100. A possible adverse effect. ACCEPTABLE. (Gee, 6/13/02).

## CHROMOSOME EFFECTS

52063 - 004, 007 136927, 186860 Murli, H. "Mutagenicity Test on Busan 85 in an *In Vitro* Cytogenetic Assay Measuring Sister Chromatid Exchange Frequencies in Chinese Hamster Ovary (CHO) Cells". (Hazleton Laboratories America, Laboratory Project ID HLA Study No.: 9970-0-438, August 6, 1987) Busan 85 (lot 7-0726, 50% a.i., 50% water) was tested at concentrations ranging from 0.005 through 0.033 µg/ml without metabolic activation for 25 hours and from 0.5 through 50.0 µg/ml with rat liver S9 Mix for 2 hours followed by 23 additional hours

of incubation before harvest by mitotic shake-off. There was a single culture per concentration and 50 cells per concentration were scored for sister chromatid exchanges. Toxicity was evaluated by percent confluent by visual examination and by mitotic cells/dead cells. There was no increase in the number of SCEs with Busan 85 treatment. UNACCEPTABLE (single culture per concentration), not upgradeable. (Kishiyama and Gee, 1/9/02). Record 186860 contains a letter from H. Murli of Covance, dated April 15, 2002, justifying the use of a single culture based on the lack of OECD guidelines for SCE assays. The letter also cites a publication by Soper and Galloway, *Mutation Res.* 312: 139 - 149 (1994) regarding the need for duplicate flasks for chromosome aberration assays. These statements are not relevant. Guidelines were available in 1983 from USEPA requiring duplicate cultures. UNACCEPTABLE. No new worksheet. NOTE: The potassium and sodium salts of dimethyldithiocarbamate are grouped for toxicological effects. See the combined Summary of Toxicology Data. (Gee, 6/13/02)

#### DNA DAMAGE

\*\* 52063 - 004, 007 136928, 186861 Cifone, M. A. "Mutagenicity Test on Busan 85 In the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (Hazleton Laboratories America, Inc., Laboratory Project ID HLA Study No.: 9970-0-447, November 11, 1987.) Busan 85 (lot 7-0726, 50% a.i.) was tested at concentrations from 2.5 to 2000 µg/ml. Concentrations from 2.5 to 100 µg/ml were evaluated for the ability to induce UDS in rat primary hepatocytes. Higher concentrations were too toxic for evaluation and a precipitate formed by the end of the incubation period at 500 µg/ml. Cytotoxicity was determined by trypan blue dye exclusion. Busan 85 did not induce UDS in primary rat hepatocytes at concentrations from 2.5 to 100 µg/ml with survival ranging from 108 to 77%. Evaluated as unacceptable but upgradeable with additional data on individual cultures including nuclear counts and cytoplasmic grain counts. (Kishiyama and Gee, 1/9/02) Record 186861 contains the results for each of the three replicate cultures, as requested, upgrading the study to ACCEPTABLE status with no adverse effect. No new worksheet. (Gee, 6/13/02).

#### NEUROTOXICITY

Not required at this time.

### SODIUM DIMETHYLDITHIOCARBAMATE STUDIES

#### CHRONIC TOXICITY, RAT

No study submitted.

Subchronic, rat

\*\* 152 - 021 115575 Marquis, J. .K. "90-Day Subchronic Oral Toxicity Study on Sodium Dimethyldithiocarbamate in the Rat." (Arthur D. Little, Incorporated, ADL Reference:

66301-00, April 29, 1991.) Aquatreat SDM, 40% active, was administered by gavage at doses of 0 (deionized water), 0.5, 5.0 and 250 mg/kg (equivalent to doses of 0.2, 2 and 100 mg SDDC/kg, respectively) to 10 Sprague-Dawley rats/sex/group, 5 days/week for 13 weeks. The incidence of lethargy was increased for high dose females. Liver weight was increased for high-dose females and the relative liver weight was increased for all treated male groups. Cholinesterase activity was not determined. Histopathological examination findings included atrophy of the exocrine pancreas with incidences of 0, 2, 0 and 4 for males with increasing dose and 0, 0, 1 and 1 for females. The report considered the pancreatic atrophy as unusual for younger rats and possibly but not conclusively treatment related. Based on the lack of a dose response or increase in severity over a 500-fold range of dose (0.5 to 250 mg/kg Aquatreat or 0.2 to 100 mg/kg SDDC), the finding has not been flagged as a possible adverse effect. NOEL = 5 (2) mg/kg (body weight, hematology, clinical signs in females). No adverse effects. ACCEPTABLE. (Kishiyama and Gee, 7/3/01).

#### CHRONIC TOXICITY, DOG

No study on file.

#### ONCOGENICITY, RAT

No study on file.

#### ONCOGENICITY, MOUSE

No study on file.

#### REPRODUCTION, RAT

No study on file.

#### TERATOLOGY, RAT

\*\* 152 - 022 115576 P. J. Wier. "Teratogenicity Study in Rats of MRD-86-933 (Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate)". (Exxon Biomedical Sciences, Inc., Laboratory Project ID 293334, 2/3/87; amended final report, 4/10/90). MRD-86-933 (Aquatreat SDM, 40% active SDDC), was administered by gavage at nominal doses of 0 (distilled water), 5, 50 or 500 mg/kg/day to 22 mated female Sprague-Dawley rats/group on days 6 to 15 of gestation in 5 ml/kg. Analytical doses were 3.95, 56.9 and 601 mg/kg of Aquatreat SDM with a proportional dose of SDDC. Body weight, body weight change and food consumption was significantly reduced for mid (not all intervals) and high dose groups. Excessive salivation was observed in 7/22 females in the high dose group during the dosing period. There were no effects on live fetuses, resorptions, fetal weight, or the incidence of malformations or variations. Nominal maternal NOEL = 5 mg of Aquatreat SDM/kg/day (body weight, food consumption). Nominal developmental NOEL  $\geq$  500 mg of Aquatreat/kg. ACCEPTABLE with no adverse developmental effects. (Kishiyama and Gee, 7/2/01).

152 027 126260. Same study as 115576 but an earlier version of the report and not including Appendix H..

## TERATOLOGY, RABBIT

\*\* 023 115578 Wier, P. J. "Teratogenicity Study in Rabbits of MRD-86-933 (Aquatreat SDM: Approximately 40% Sodium Dimethyldithiocarbamate)". (Exxon Biomedical Sciences, Inc., Laboratory Project ID 293334RB, 2/27/87) MRD-86-933 (Aquatreat SDM, 40% active Sodium dimethyldithiocarbamate, SDDC), was administered by gavage at doses of 0 (distilled water), 1, 10 or 100 mg/kg (equivalent to 0.4, 4, or 40 mg/kg SDDC) to 18 artificially inseminated New Zealand female rabbits/group on days 7 to 19 of gestation. Body weight and body weight gains were reduced sporadically for the high dose group compared with controls but the initial mean body weight was 5% lower at day 0, so that a meaningful comparison was difficult. Food intake was reported as "little or no apparent food consumption" at 100 mg/kg during the last week of dosing (incidences of 0, 1, 4 and 6\* with increasing dose). A preliminary study, with 5 does/dose, indicated that 250 and 500 mg/kg Aquatreat SDM were effect levels, based on females with complete embryo loss at 250 (3) and 500 (2) and a significant body weight affect at 500 mg/kg. Therefore, the maternal NOEL = 100 mg/kg Aquatreat SDM, equivalent to 40 mg/kg SDDC. Developmental NOEL = 100 mg/kg Aquatreat SDM, with no effects on fetal survival, malformations or variations. ACCEPTABLE with no adverse effect. (Kishiyama and Gee, 7/18/01).

## GENE MUTATION

\*\* 50320-001 045560, "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", Study No. T4305.501, Microbiological Associates, Inc., Bethesda, MD, 1/2/86. The reversion rate of *Salmonella typhimurium* (tester strains TA98, TA100, TA1535, TA1537, TA1538) from histidine auxotrophy to prototrophy was measured by the plate incorporation technique in the presence of Sodium Dimethyldithiocarbamate (lot # 37219, 40% stated purity) at 0, 10, 100, 333, 1000, or 3333 µg/plate with or without metabolic activation system (S9 fraction of Aroclor 1254 induced male Sprague-Dawley rat liver homogenates). A **possible adverse effect** was indicated by increased reversion rates with or without activation. The study was upgraded from unacceptable (H. Green and S. Morris, 6/4/91) to acceptable by submission of an adequate statement of purity (S. Morris and J. Gee, 2/28/92).

50320-002 This document contains an exact duplicate of 50320-001 045560. No worksheet was done (S. Morris, 6/4/91).

152-014 041550: This document contains an exact duplicate of 50320-001 045560. No worksheet was done (S. Morris, 6/4/91).

A letter dated 01/27/92 (no doc. or rec. #'s, ID# SBDR-132663-E) contains an adequate statement of purity and lot number.

152 - 028 126261: Exact duplicate of 50320-001 045560. No worksheet. (Kishiyama, 9/18/00).

**50320-001 045563** "CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation, Test Article, Sodium Dimethyldithiocarbamate, Final Report", MA Study No. T4305.332, Microbiological Associates, Inc., Bethesda, MD., 1/30/86. The forward mutation rate at

the HGPRT locus was measured in K1-BH4 Chinese Hamster ovary cells by selection for 6-thioguanine resistant growth after exposure to sodium dimethyldithiocarbamate (lot # 37219, 40% stated purity) in the presence of metabolic activation (S9 fraction of Aroclor induced male Fischer rat liver homogenate) at 0, 0.1, 0.4, 0.7, 1.0, or 1.5 nl/ml and without activation at 0, 0.007, 0.01, 0.04, 0.07, or 0.1 nl/ml. A **possible adverse effect** was indicated by increased forward mutation rates under non-activated conditions. The study was UNACCEPTABLE and not upgradeable because there was only one sample per treatment group and no confirmation trial (H. Green and S. Morris, 06/26/91).

50320-002 This document contains an amended duplicate of 50320-001 045563. No worksheet was done (S. Morris, 06/26/91).

152-016 042291: This document contains an amended duplicate of 50320-001 045563. No worksheet was done (S. Morris, 06/26/91).

A letter dated 01/27/92 (no doc. or rec. #'s) contains an adequate statement of purity and lot number.

152 028 126262: Exact duplicate of 50320-001 045563. No worksheet. (Kishiyama, 9/18/00).

## CHROMOSOME EFFECTS

**50320-001 045561**, "Chromosome Aberration Assay in Chinese Hamster Ovary (CHO) Cells, Test Article, Sodium Dimethyldithiocarbamate, Final Report", Study No. T4305.337, Microbiological Associates, Inc., Bethesda, MD., 12/9/85. Sodium Dimethyldithiocarbamate (lot # 37219, 40% stated purity) was tested in a chromosome aberration assay in which duplicate cultures of Chinese Hamster ovary cells were treated in the presence of metabolic activation (S-9 fraction from Aroclor 1254 induced adult male Sprague-Dawley rat liver homogenates) at 0, 1.0, 3.0, 10.0, and 20.0 nl/ml and absence at 0, 0.1, 0.3, 1.0, and 3.0 nl/ml. A **possible adverse effect** was indicated by increased chromosome aberrations at 20 nl/ml in the presence of metabolic activation. The study is UNACCEPTABLE and not upgradeable because there was insufficient time for expression of chromosomal damage (S. Morris and H. Green, 6/7/91).

152-014 041551: This document contains an exact duplicate of 50320-001 045561. No worksheet was done (S. Morris, 6/7/91).

50320-002 This document contains an exact duplicate of 50320-001 045561. No worksheet was done (S. Morris, 6/7/91).

A letter dated 01/27/92 (no doc. or rec. #'s) contains an adequate statement of purity and lot number.

152 – 028 126263 Duplicate study of 045561. No worksheet. (Gee, 7/24/01)

50320-001 045562, "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells, Test Article, Sodium Dimethyldithiocarbamate, Final Report", MA Study No. T4305.334, Microbiological Associates, Inc., Bethesda, MD., 1/27/86. Sodium

dimethyldithiocarbamate (lot # 37219, 40% stated purity) was tested for induction of sister chromatid exchanges in cultured Chinese Hamster ovary cells. The assay was performed in duplicate in the presence of exogenous metabolic activation (S9 fraction of Aroclor 1254 induced adult, male Sprague-Dawley rat liver homogenates) at 0, 1.0, 3.0, 10.0, or 20.0 nl/ml or without activation at 0, 0.1, 0.3, 1.0, or 3.0 nl/ml. No adverse effect was indicated. The study was UNACCEPTABLE and not upgradeable because the exposure protocol without activation did not allow for sufficient cellular replication in the presence of BrdU (H. Green and S. Morris, 06/21/91).

Note: Although the evaluation of record 045562 was correct technically, there were several of the lower concentrations for which data could be obtained (0.1 and 0.3 nl/ml) for M2 cells.

These were negative for SCEs. With activation, all concentrations yielded sufficient cells for scoring and were negative. See the original review by Green and Morris for details. The study with potassium dimethyldithiocarbamate was faulted for the use of a single culture per concentration. While this is not according to US EPA guidelines in effect at the time of study conduct, those results for the SCE assay were also negative. (Gee, 6/14/02)

50320-002 This document contains an exact duplicate of 50320-001 045562. No worksheet was done (S. Morris, 06/21/91).

152-016 042290 This document contains an exact duplicate of 50320-001 045562. No worksheet was done (S. Morris, 06/21/91).

A letter dated 01/27/92 (no doc. or rec. #'s) contains an adequate statement of purity and lot number.

152-028 126264: Exact duplicate of 50320-001 045562. No worksheet. (Kishiyama, 9/18/00).

#### DNA DAMAGE

\*\* 024 121316 "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography", (K. J. Pant, SITEK Research Laboratories, SITEK Study No.: 0215-5100, 2/22/93.) Aquatreat SDM (sodium dimethyldithiocarbamate, SDDC, purity 38.9%), was tested for induction of unscheduled DNA synthesis at concentrations of 0 (medium, water or ethanol), 0.5, 1.0, 2.0, 4.0, 6.0 and 8.0 µg/ml in the first assay and at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 µg/ml in a second assay with primary rat hepatocytes exposed for 18 hours. Cell survival for the two highest treatment groups (6 and 8 µg/ml and 5 and 6 µg/ml) was 0%. Other SDDC treatment groups did not induce unscheduled DNA synthesis in either assay. ACCEPTABLE with no adverse effect. (Kishiyama and Gee, 7/19/01).

#### NEUROTOXICITY

Not required at this time.

#### OTHER

Subchronic, Rabbit:

\*\* 152 - 026, 036 126257, 186916 Plutnick, R. T. "Subchronic Dermal Toxicity Study in the Rabbit (Aquatreat SDM - Sodium dimethyldithiocarbamate)" (EXXON Biomedical Sciences, Inc., Laboratory Project ID 293310, 12/30/86, supplemental data submitted 4/22/02). Aquatreat SDM (100% assumed for Batch 1) was administered undiluted by dermal application at doses of 0, 50, 150, or 300 mg/kg to 10 New Zealand White rabbits/sex/group. [This batch contained 40% a.i. so that the actual doses were 20, 60 and 120 mg/kg/day]. pH was greater than 12 with a density of 1.18 g/ml, used in calculating dosing volumes. Applications were for 6 hours per day, 5 days per week for 13 weeks. MRD-86-933 treatment was associated with an increased incidence of dermal irritation at all doses but particularly at the mid and high doses where all animals showed edema, reddening and desquamation at some time during the study. The incidences tended to decrease as the study progressed. The high pH of the test article was probably a factor. These findings were confirmed by histopathology effects of diffuse acanthosis and hyperkeratosis. Dermal NOEL < 50 mg/kg/day Aquatreat SDM. WBC and platelet counts decreased for the high dose group when measured at study termination. Systemic NOEL = 150 mg/kg Aquatreat SDM. Evaluated as unacceptable (range-finding study for dose selection, information regarding the method of dosing undiluted test article and the meaning of "N" in a table.) (Kishiyama and Gee, 7/2/01). Record 186916 contained revised table 1 with "N" = 10, the number of animals per sex examined, rather than those with some finding. The application method was explained as based on the water solubility of the test material and an attempt to prevent loss of a dose by applying to the one-ply gauze inside the occlusive sleeve rather than the skin. The amount of surface area actually covered by a dose after wicking into the gauze was not measured. Because of the aqueous nature of the test article, this method was not unreasonable. Upgraded to ACCEPTABLE status. (Gee, 6/13/02)